EXTENDED REPORT

Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis

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Background: Rheumatoid arthritis is associated with increased cardiovascular mortality and morbidity.
Objective: To assess the effect of severe extra-articular rheumatoid arthritis (ExRA) manifestations on the risk of cardiovascular disease (CVD) in patients with rheumatoid arthritis.
Methods: Patients with ExRA (n = 81) according to predefined criteria and controls (n = 184) without evidence of extra-articular disease were identified from a large research database of patients with rheumatoid arthritis. In a structured review of the medical records, the occurrence and the date of onset of clinically diagnosed CVD events were noted. Cox proportional hazards models were used to estimate the effect of ExRA on the risk of first ever CVD events after the diagnosis of rheumatoid arthritis. ExRA manifestations were modelled as time-dependent covariates, with adjustment for age, sex and smoking at the diagnosis of rheumatoid arthritis. Onset of erosive disease and rheumatoid factor seropositivity were entered as time-dependent variables. Patients were followed until onset of CVD, death or loss to follow-up.
Results: ExRA was associated with a significantly increased risk of first ever CVD events ($p<0.001$), and also with an increased risk of new-onset coronary artery disease, adjusted for age, sex and smoking (hazard ratio (HR): 3.16; 95% confidence interval (95% CI: 1.58 to 6.33). The association between ExRA and any first ever CVD event remained significant when controlling for age, sex, smoking, rheumatoid factor and erosive disease (HR: 3.25; 95% CI: 1.59 to 6.64).
Conclusion: Severe ExRA manifestations are associated with an increased risk of CVD events in patients with rheumatoid arthritis. This association is not due to differences in age, sex, smoking, rheumatoid factor or erosive joint damage. It is suggested that systemic extra-articular disease is a major determinant of cardiovascular morbidity in rheumatoid arthritis.

Rheumatoid arthritis is associated with an increased mortality compared with the general population,[1–3] in particular from cardiovascular disease (CVD).[4–6] The extent of comorbidity in patients with rheumatoid arthritis has been insufficiently studied in the past, but recent studies have highlighted an increased incidence of CVD events in patients with rheumatoid arthritis.[7–9] The increase in vascular morbidity appears to be mainly due to an excess of myocardial infarctions, whereas the risk of stroke in patients with rheumatoid arthritis may not be significantly different from that expected.[8 9]

Predictors of mortality in rheumatoid arthritis include measures of disability,[10] signs of disease activity and joint damage,[2] positive rheumatoid factor[11] and severe extra-articular disease manifestations.[3 12–15] In a study of a community-based rheumatoid arthritis cohort, mortality was markedly increased in patients with severe extra-articular rheumatoid arthritis (ExRA) compared with patients without ExRA, after adjusting for age, sex and comorbidities.[15] This indicates that ExRA has a major effect on survival in rheumatoid arthritis.

ExRA manifestations have been associated with an increased risk of serious infections[16] and gastrointestinal bleeding.[17] In a study which included investigation of cause-specific mortality, the poor survival in patients with ExRA was mainly due to an increased number of deaths from CVD compared with that expected.[14] A recent survey confirmed that some ExRA manifestations are associated with increased cardiovascular mortality.[18] The effect of ExRA on the total risk of fatal and non-fatal CVD events has not been investigated. Also, the relative effect of ExRA and other measures of disease severity in rheumatoid arthritis on co-morbidity and mortality requires further investigation.

Examination of the relationship between disease-associated factors and vascular comorbidity in patients with rheumatoid arthritis require long-term follow-up, with a careful and consistent assessment of disease expression and CVD end points. The purpose of this study was to examine the risk of CVD in a well-characterised cohort of patients with ExRA compared with controls without ExRA, adjusting for potential confounders, including smoking.

METHODS

Patients and outcomes

Patients (n = 81) with severe ExRA according to predefined criteria, including clinically diagnosed pericarditis, pleuritis, Felty's syndrome, polyneuropathy, mononeuropathy, scleritis, episcleritis, glomerulonephritis, major cutaneous vasculitis and vasculitis involving other organs, each supported by objective findings and with other causes unlikely or excluded,[15 19] were identified from a research database of patients with rheumatoid arthritis seen at the Mayo Clinic, Rochester, Minnesota, USA. The date of first documented severe ExRA manifestation was noted. The year of first diagnosis of ExRA ranged from 1964 to 2002, with 75% of patients being diagnosed with ExRA in 1990 or later. A random sample, stratified by sex, of patients from the database without a record of ExRA manifestations was

Abbreviations: CVD, cardiovascular disease; ExRA, extra-articular rheumatoid arthritis

Table 1 Criteria for cardiovascular events in patients with rheumatoid arthritis

1. MI	Definite MI based on history, ECG and cardiac enzymes[21 22]
2. Angina pectoris	History of typical chest pain with compatible ECG or myocardial scintigraphy, stress ECG or stress echocardiogram
3. Haemorrhagic stroke	Clinical diagnosis verified by CT or autopsy
4. Non-haemorrhagic or non-specified stroke	(A) Clinical diagnosis by a neurologist or (B) clinical diagnosis verified by CT or autopsy
5. Transient ischaemic attack	Clinical diagnosis
6. Amaurosis fugax	Clinical diagnosis
7. Aortic aneurysm	(A) Diameter increased >50% compared with normal or (B) diameter >3.0 cm in abdominal aorta[21] Verified by ultrasound/CT or at autopsy
8. Renal artery stenosis	Verified by ultrasound/renal scintigraphy/angiography
9. PVD or atherosclerosis obliterans	(A) Clinical diagnosis (supported by documented vascular physical examination) and (B) ankle/brachial index <0.9 or angiography confirming PVD if performed
10. Arterial thromboembolism	Clinical diagnosis supported by angiography or autopsy

CT, computed tomography; ECG, electrocardiogram; MI, myocardial infarction; PVD, peripheral vascular disease.

reviewed. Controls (n = 184) without any evidence of extra-articular disease (including rheumatoid nodules) were identified. All patients with ExRA and controls fulfilled the 1987 ACR criteria for rheumatoid arthritis.[20] The date of diagnosis was defined as the first date of fulfilment of the rheumatoid arthritis criteria. The year of rheumatoid arthritis diagnosis ranged from 1939 to 2001, with 74% of the patients being diagnosed in 1985 or later.

In a structured review of the medical records of the Mayo Clinic, as well as external records present in the Mayo charts, the occurrence and date of onset of clinically diagnosed CVD events (according to predefined criteria; table 1: myocardial infarction, angina pectoris, haemorrhagic stroke, non-haemorrhagic or non-specific stroke, transient ischeamic attack, amaurosis fugax, aortic aneurysm, renal artery stenosis, peripheral vascular disease or atherosclerosis obliterans, and arterial thromboembolism) were recorded by one of the authors (CT). Myocardial infarctions were classified using standard algorithms.[22 23] In addition, CVD events were classified according to the Antiplatelet Trialists' Collaboration composite CVD end points of myocardial infarction, stroke (ischaemic and haemorrhagic) and cardiovascular death.[24] Data on smoking at the onset of rheumatoid arthritis, documentation of onset of erosive disease and positive rheumatoid factor tests were extracted from the medical records. The date of the last documented physical examination was noted as the date of last follow-up.

Statistical analysis

The sex distribution, number of smokers at the diagnosis of rheumatoid arthritis, number of patients with a positive rheumatoid factor test and number of patients with documented joint erosions were compared between those with and without ExRA manifestations using the χ^2 test. Age at diagnosis of rheumatoid arthritis, length of follow-up, time to first positive rheumatoid factor test in those ever positive and time to first documented erosion in those with erosions were compared using t tests. Cox proportional hazards models were used to estimate the effect of ExRA on the risk of first ever CVD events (see below) after diagnosis of rheumatoid arthritis. Patients with documented first onset of CVD before diagnosis of rheumatoid arthritis were excluded from the analysis. The ExRA manifestations were modelled as time-dependent covariates, with adjustment for age, sex and smoking. Patients with data missing on smoking history were excluded from the multivariate analysis. Further, onset of erosive disease and rheumatoid factor seropositivity were entered as time-dependent variables. A Kaplan–Meier analysis was performed to estimate survival free of cardiovascular disease after ExRA compared with patients with rheumatoid arthritis and controls, allowing patients to transfer from the non-ExRA group to the ExRA group to incorporate the time-varying nature of ExRA manifestations. Patients were followed until onset of CVD, death or loss to follow-up.

These analyses were performed for the first CVD event combined (table 1), for the first coronary artery disease event (criteria 1 and 2, table 1) and for the first cerebrovascular event (criteria 3–6, table 1) separately. In these subanalyses, patients with a documented history of the corresponding events before the diagnosis of rheumatoid arthritis were excluded from the analyses, but not patients with other previous CVD events. For example, patients with onset of angina before the diagnosis of rheumatoid arthritis were excluded from the analysis of new-onset coronary artery disease, but not from the analysis of new-onset cerebrovascular disease.

RESULTS

In all, 81 patients with ExRA and 184 controls were studied. In the ExRA subgroup, 25 patients had a history of major cutaneous vasculitis, 5 had biopsy-verified vasculitis involving other organs, 12 had pleuritis, 13 had pericarditis, 12 had Felty's syndrome, 9 had peripheral mononeuropathy, 22 had peripheral polyneuropathy, 4 had severe ophthalmological manifestations (scleritis, episcleritis or retinal vasculitis) and 1 had glomerulonephritis. The mean duration of rheumatoid arthritis at the time of ExRA diagnosis was 9.5 years (standard deviation (SD) 8.8, range 0–30.1). Age at onset of rheumatoid arthritis was similar among patients with and without ExRA (table 2). There was a male predominance among ExRA cases,

Table 2 Demographic and clinical data in patients with ExRA *v* patients without ExRA

	ExRA	Non-ExRA	
n	81	184	p Value
Year of RA diagnosis	1939–2000	1947–2001	
Age at RA diagnosis (years; mean (SD))	51.0 (13.8)	50.6 (16.1)	0.86
Sex (male/female)	45/36	91/93	0.36
Follow-up time (years; mean (SD))	15.6 (10.7)	7.8 (8.7)	<0.001
Smokers at RA diagnosis	49.3%	27.4%	0.001
RF positive at any time (%)	92.6%	59.2%	<0.001
Erosive disease (%)	71.6	47.8	<0.001

ExRA, extra-articular rheumatoid arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 3 Cardiovascular events in patients with and without ExRA

	ExRA group (n = 81)		
	Total	After ExRA diagnosis	Non-ExRA group (n = 184)
Myocardial infarction	9	6	6
Angina pectoris	21	16	12
Haemorrhagic stroke	0	0	1
Non-haemorrhagic stroke	4	3	2
TIA	3	3	4
Amaurosis fugax	1	1	0
Aortic aneurysm	3	3	2
Renal artery stenosis	3	3	0
Peripheral vascular disease	9	9	1
Arterial thromboembolism	2	1	0

ExRA, extra-articular rheumatoid arthritis; TIA, transitoric ischaemic attack.

but the sex distribution was not significantly different from that of controls. The average follow-up time was longer in patients with ExRA than in controls with rheumatoid arthritis (mean 15.6 *v* 7.8 years, p<0.001). Patients with ExRA were more likely to be smokers at the diagnosis of rheumatoid arthritis (49.3% *v* 27.4%; p = 0.001), to be rheumatoid factor positive (92.6% *v* 59.2%; p<0.001) and to have documented evidence of erosive joint disease (71.6% *v* 47.8%; p<0.001).

In all, 15 patients had a documented history of CVD before the diagnosis of rheumatoid arthritis, and were thus excluded from the analysis. First ever CVD events occurred in 49 patients after the diagnosis of rheumatoid arthritis, and 34 of these were in patients with ExRA. Among patients with ExRA, 8 (23%) of these 34 events occurred after onset of rheumatoid arthritis but before the diagnosis of ExRA, and in the remaining 26 (77%) after the diagnosis of ExRA. New onset coronary artery disease was identified in 44 patients (28 with ExRA, with 6 events (21%) occurring before the diagnosis of ExRA and 22 (79%) after the diagnosis of ExRA). There were 12 cases of new-onset cerebrovascular disease (7 among patients with ExRA, with 1 presenting before the diagnosis of ExRA and 6 after the diagnosis of ExRA). Table 3 shows the distribution of individual first ever CVD events after the diagnosis of rheumatoid arthritis. Data on smoking were available for 250 patients (75 with and 175 without ExRA).

The survival free of CVD was markedly lower after ExRA compared with patients with rheumatoid arthritis and absence of ExRA manifestations (fig 1). In the unadjusted analysis,

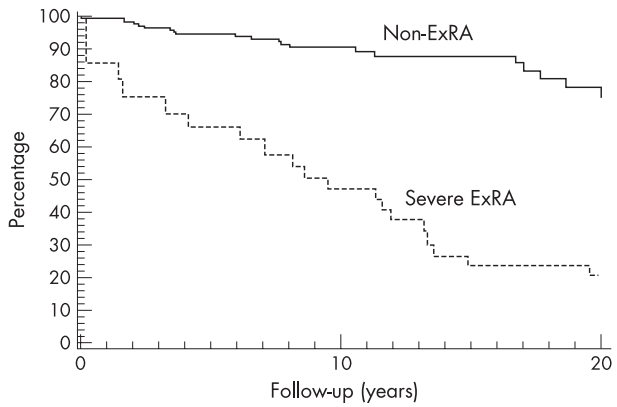

Figure 1 Survival free of cardiovascular disease after severe extra-articular disease manifestations compared with patients with rheumatoid arthritis and no severe extra-articular disease. ExRA, extra-articular rheumatoid arthritis.

ExRA, male sex, age, smoking, rheumatoid factor and erosive disease were all significant predictors of first ever CVD events (table 4). The presence of ExRA was associated with an increased risk of both coronary artery disease (p<0.001) and cerebrovascular disease (p = 0.040; table 5). In models adjusted for age, sex and smoking, ExRA continued to be a predictor of first ever CVD events (hazard ratio (HR): 3.78; 95% confidence interval (95% CI): 2.00 to 7.16) and of new onset coronary artery disease (HR: 3.16; 95% CI: 1.58 to 6.33). The number of cerebrovascular events was considered to be insufficient for a separate multivariate analysis of cerebrovascular disease.

The association between ExRA and any first ever CVD event remained significant on controlling for age, sex, smoking, rheumatoid factor and erosive disease (HR: 3.25; 95% CI: 1.59 to 6.64). Smoking, rheumatoid factor and erosive disease increased the risk of new-onset CVD significantly in the univariate analysis, but not in the fully adjusted model (table 6). Male sex (p<0.001) and higher age (p<0.001) continued to be associated with first ever CVD events in the multivariate models. In models adjusted for age, sex and smoking, rheumatoid factor was a significant predictor of first ever CVD events (HR: 2.33; 95% CI: 1.14 to 4.78), whereas the association between erosive joint disease and new onset CVD did not reach significance (HR: 1.84; 95% CI: 0.93 to 3.68).

In all, 25 patients fulfilled the Antiplatelet Trialists' Collaboration composite CVD end point of myocardial infarction, stroke or cardiovascular death after diagnosis of rheumatoid arthritis. Fifteen of these patients had severe extra-articular disease, with 11 of 15 events occurring after ExRA onset. Severe ExRA was associated with an increased risk of this end point (HR: 2.84; 95% CI: 1.17 to 6.88), with a similar trend after adjustment for age and sex (HR: 1.97; 95% CI: 0.78 to 4.96).

DISCUSSION

To our knowledge, this is the largest cohort of patients with severe ExRA in which the relationship between ExRA and CVD has been systematically evaluated. Severe ExRA manifestations were associated with an increased risk of new-onset CVD in patients with rheumatoid arthritis. The increased incidence of first ever CVD events in the group with ExRA was mainly due to an excess of patients with onset of coronary artery disease after the diagnosis of ExRA. The association between ExRA manifestations and coronary artery disease, and the association of ExRA with CVD overall, remained significant on adjusting for age, sex and smoking, indicating that none of these potential confounders explain the increased cardiovascular co-morbidity in patients with ExRA. Further, we showed that rheumatoid factor and erosive joint damage are both associated with increased CVD morbidity, and that the effect of rheumatoid factor was not secondary to smoking. However, the effect of ExRA, but not that of rheumatoid factor and erosive disease, remained significant in the multivariate model. This suggests that CVD in rheumatoid arthritis may be specifically associated with systemic disease involving extra-articular organs, rather than with disease severity in general.

Our findings are in accordance with previous studies, in which an increased mortality from CVD associated with ExRA manifestations was found in one hospital-based cohort[14] and in one community-based cohort[18] of patients with rheumatoid arthritis, but go further in defining the nature of this relationship. They also confirm that the comorbidities that underlie the premature death in ExRA are not due to confounding by smoking. The estimated more than threefold increase of CVD incidence in ExRA compared with patients with non-ExRA rheumatoid arthritis is compatible with the observed markedly impaired survival in patients with ExRA, whereas mortality in

Table 4 Predictors of first ever cardiovascular event in patients with rheumatoid arthritis; univariate analysis

	Hazard ratio	95% CI	p Value
Age (per year)	1.08	1.06 to 1.11	<0.001
Male sex	3.95	2.09 to 7.46	<0.001
Smoking at RA diagnosis	2.14	1.20 to 3.82	0.010
Severe ExRA manifestation	5.65	3.10 to 10.31	<0.001
Positive RF	3.90	1.99 to 7.65	<0.001
Erosions	2.42	1.29 to 4.55	0.006

ExRA, extra-articular rheumatoid arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor.

patients without ExRA has not been found to be significantly different from that in the general population.[15] In addition, our results support the concept that ExRA manifestations precede the occurrence of CVD morbidity. With respect to assessment of causality, our findings suggest that it is more likely that pathogenetic mechanisms involved in ExRA initiate or accelerate vascular pathology, than that vascular disease predisposes to severe ExRA manifestations.

Rheumatoid factor has been shown to be related to cardiovascular mortality in early inflammatory polyarthritis[25] and to overall mortality in patients with established rheumatoid arthritis.[11] Furthermore, ''false positive'' rheumatoid factor has also been associated with cardiovascular mortality in the general population.[26] Our study confirms that rheumatoid factor is related to CVD in patients with rheumatoid arthritis, but the presence of rheumatoid factor did not account for the robust association between ExRA and CVD.

The importance of inflammation in atherosclerotic vascular disease is increasingly recognised. Inflammatory biomarkers such as high-sensitivity C reactive protein[27–29] or other inflammation-sensitive plasma proteins[30] are predictors of CVD in the general population. Atherosclerotic lesions in coronary artery disease are characterised by inflammatory cell infiltrates.[31] In systemic lupus erythematosus (SLE), an even greater excess morbidity from CVD than in rheumatoid arthritis has been found,[32] and CVD events are associated with high SLE disease activity.[33] In patients with rheumatoid arthritis, raised ESR[34] and C reactive protein[35] have predicted CVD comorbidity. The suggested shared disease mechanism in rheumatoid arthritis and CVD includes clonal expansion of immunosenescent T cells[36 37] and systemic endothelial activation,[38] both of which are particularly associated with ExRA. Severe ExRA includes a wide spectrum of clinical manifestations, and the pathogenetic mechanisms involved may vary for different disease features. We have recently shown that patients with severe ExRA have an increased risk of developing symptomatic peripheral arterial disease and an increased risk of venous thromboembolic events.[39] This suggests that immunological and inflammatory abnormalities in ExRA contribute to increased atherosclerosis, and also have an effect on blood clotting. The importance of endothelial activation[38] and other vascular pathomechanisms in rheumatoid arthritis should be further explored. Our study suggests that patients with rheumatoid factor-positive rheumatoid arthritis are at an increased risk of CVD, but that patients with severe ExRA have the highest risk of developing new CVD events. Based on this, increased awareness of the risk of CVD and preventive measures such as treatment with statins and low-dose aspirin should be considered in subjects without a history of vascular disease, in patients with rheumatoid factor-positive rheumatoid arthritis and in patients with severe ExRA.

Limitations of our study include its retrospective design, which confines the analysis to clinical data available from the medical records. For the CVD events, we chose criteria that rely on clinical findings and objective verification. Although these criteria may not identify all patients with discrete signs and symptoms of CVD, they should identify most of the patients with severe coronary artery and cerebrovascular events. A random misclassification of patients with undiagnosed CVD would decrease the likelihood of detecting true differences between the groups.

The follow-up time was longer in patients who developed ExRA than for the controls. This is an inherent feature of the design in which subjects with longer follow-up are more likely to develop ExRA at some point. They are also more likely to develop CVD events, which makes the time-dependent analysis critical. There is also a potential concern for some detection bias in our findings—that is, subjects who have ExRA manifestations may return for follow-up more frequently, and hence events may be more likely to be detected in this group. As our end points are severe cardiovascular events, this bias is probably minimal.

The criteria for severe ExRA manifestations were originally developed for retrospective chart reviews,[14 15] and should capture most of the clinically relevant manifestations. As rheumatoid nodules predict severe ExRA,[40 41] a control group of non-nodular patients is less likely to include patients with undiagnosed ExRA. Still, misclassification may occur in individual patients. However, any misclassification of patients with actual extra-articular disease as non-ExRA controls would tend to attenuate rather than enhance the differences between the groups in our study.

As other indicators of disease severity, we chose markers which are consistently recorded for patients with rheumatoid arthritis—rheumatoid factor positivity and the presence of joint erosions. Owing to the nature of the study, we could not assess the effect of disability or disease activity, including inflammatory biomarkers such as C reactive protein, on the risk of CVD. The relative importance of these factors and ExRA for CVD comorbidity is therefore still unknown. Furthermore, we were

Table 5 Effect of severe ExRA on first ever cardiovascular events in patients with RA

Patients analysed (n)*	ExRA group (n = 81)	Total	After ExRA diagnosis	Non-ExRA group (n = 184)	Hazard ratio	95% CI	p Value
Coronary artery disease	253	29	22	16	4.62	2.43 to 8.76	<0.001
Cerebrovascular disease	263	7	6	5	3.77	1.06 to 13.43	0.040
Any CVD event	250	34	26	15	5.65	3.10 to 10.31	<0.001

CVD, cardiocvascular disease; ExRA, extra articular rheumatoid arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor.
*Patients with first event (of coronary artery disease, cerebrovascular disease or any CVD) before RA diagnosis were excluded.

Table 6 Predictors of first ever cardiovascular event in patients with rheumatoid arthritis (multivariate analysis)*

	Hazard ratio	95% CI	p Value
Age (per year)	1.10	1.06 to 1.14	<0.001
Male sex	3.59	1.78 to 7.24	<0.001
Smoking at RA diagnosis	1.53	0.80 to 2.95	0.20
Severe ExRA manifestation	3.25	1.59 to 6.64	0.001
Positive RF	1.52	0.67 to 3.42	0.32
Erosions	1.02	0.46 to 2.26	0.97

ExRA, extra-articular rheumatoid arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor.
*The model is adjusted for all included variables.

unable to analyse the effect of treatment-related factors and traditional CVD risk factors beyond age, sex and smoking, such as diabetes, hypertension and hyperlipidaemia. Others have, however, shown that the overall excess CVD morbidity in rheumatoid arthritis is not explained by traditional risk factors, indicating that disease-related factors are more important.[7 8] A recent analysis of factors associated with an excess risk of heart failure in patients came to similar conclusions.[42] We cannot exclude that differences in traditional CVD predictors other than smoking between patients with and without ExRA explain our results. Further, given the wide range in the year of diagnosis of rheumatoid arthritis, changes in the disease process over time could influence the assessment of CVD comorbidity. Our findings should therefore be confirmed in prospective investigations, with assessment of all potential confounders, and analysis of the effect of other disease activity measures and treatment on the risk of CVD.

Patients were identified for inclusion into this study on the basis of the presence of ExRA without systematic exclusion criteria. The study was performed at a major referral centre. Our findings are therefore not immediately generalisable to other populations with rheumatoid arthritis. On the other hand, our findings are consistent with studies of CVD mortality in well-defined samples,[14 18] and provide an estimate of the relative importance of ExRA and other factors in a high-risk population.

In conclusion, we have shown an increased incidence of coronary artery disease and other CVD events in patients with ExRA compared with non-ExRA controls without ExRA with rheumatoid arthritis, and shown that this association is not due to differences in age, sex, smoking, rheumatoid factor or erosive joint damage. We suggest that systemic extra-articular disease is a major determinant of cardiovascular morbidity in rheumatoid arthritis.

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